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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/207,649	12/08/1998	SUSAN LINDQUIST	ARCD:278	7099

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EXAMINER	
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ART UNIT	PAPER NUMBER
1647	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/207,649	Lindquist
Examiner	**Art Unit**
Sharon L. Turner, Ph.D.	1647

-- Th MAILING DATE of this communication appears on th cover sheet with the correspondenc address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on 2-12-02

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) 1, 3, 7-20, 22, and 37-40 is/are pending in the applica

4a) Of the above, claim(s) 38-40 is/are withdrawn from considera

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) 1, 3, 7-20, 22, and 37 is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☒ Claims 1, 3, 7-20, 22, and 37-40 are subject to restriction and/or election requirem

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
18) ☐ Interview Summary (PTO-413) Paper No(s). _____
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

DETAILED ACTION

1. Upon further consideration, the finality of the previous office action is withdrawn. It is noted that a Notice of Appeal and Appeal Brief have been filed. Applicant can request a refund for the associated fees or leave it as credit for future appeals.

2. Claims 1, 3, 7-20, 22 and 37-40 are pending.

3. Claims 38-40 remain directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: New claims 38-40 are drawn to methods of identifying candidate substances that inhibit the formation of amyloid fibrils. This is in contrast to methods of identifying candidate substances that inhibit the formation of amyloid aggregates. Fibrils are distinct structures from aggregates because fibrils are ordered structures of beta amyloid found in Alzheimer's brains and exhibit rod-like and beta-sheet conformations. In contrast, aggregates merely constitute clustered, closely associated or bound proteins.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 38-40 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Claim Objections

4. Claims 7-11 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the

claim(s) in independent form. In the instant case, claim 1 requires a "protein" or "peptide". Dependent claim 7 requires less than (not all the limitations of) claim 1, because the "aggregate forming domain" as recited in claim 7 is but a portion of the "peptide" or "protein" of claim 1. Thus, claim 7 does not share all of the limitations of claim 1. Claim 7 broadens the scope of independent claim 1 because requiring only the aggregate forming domain of the protein or peptide leaves more variability in those sequences which are required. In addition, a reference which taught the a shorter chimeric aggregate forming domain but not a chimeric of the full length peptide could meet the limitations of claim 7 but not claim 1, which is not permitted. Thus, claim 7 does not further limit claim 1, but instead broadens the scope of the claims.

Specification

5. The disclosure is objected to because of the following informalities: The amendment directing correction of the priority data in the communication of 11-10-99 has resulted in the duplication of material. Applicants should direct that lines 2-6 of page 2 be deleted to remove the inappropriate material.

Appropriate correction is required.

6. The disclosure is objected to because of the following informalities:

Applicant may be his or her own lexicographer as long as the meaning assigned to the term is not repugnant to the term's well known usage. In re Hill, 161 F.2d 367, 73 USPQ 482 (CCPA 1947). Any special meaning assigned to a term "must be sufficiently clear in the specification that any departure from common usage would be so understood

by a person of experience in the field of the invention." Multiform Desiccants Inc. v. Medzam Ltd., 133 F.3d 1473, 1477, 45 USPQ2d 1429, 1432 (Fed. Cir. 1998).

In the instant case applicants have used the terms "aggregate-prone amyloid protein/peptide" , "aggregated amyloid formation" and "aggregation" in the claims. However, as described in the specification at p. 5, lines 16-22, such peptides, "may be any protein that is able to form an amyloid or amyloid-like deposit" and further, "that a protein of essentially any origin may be used in the present invention". Functionally, the, "amyloid or amyloid like deposits are generally insoluble fibrillary material...aggregate under physiological conditions... and include yeast proteins such as Sup35 and URE3." Thus, while the artisan recognizes specific amyloid peptides/proteins and specific amyloid aggregates, plaques, fibrils or formations the use of the terms to describe alternative peptides/proteins and their particular interactions is repugnant in the art.

In addition, applicants have used the term "chimeric" in the claims. However, the specification at p. 5, lines 25-28 defines a chimeric protein to be that , "the protein comprises polypeptides which do not naturally occur together in a single protein unit." Thus, in contrast to the art recognize term of chimeric proteins as referring to fusion proteins, the term chimeric peptide as used in the claims encompasses any non-naturally occurring peptide including altered or mutated proteins which do not naturally occur. Thus, while the artisan recognizes chimeric fusion proteins, the use of the terms to describe any non-naturally occurring peptide is repugnant in the art.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 1, 3, 7-20, 22 and 37 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The terms "aggregate-prone amyloid peptide" and "aggregate-prone amyloid protein" as used in claim 1 are indefinite because the recitations are not the same and the artisan cannot readily discern the difference, if any in the scope of the two terms. As peptides are generally but not necessarily smaller in length than proteins or polypeptides, and the specification fails to define the different terms, it is unclear whether or not the "peptides" or "proteins" are the same or are of different scope, i.e., are different in sequence and/or length.

The terms "β-amyloid polypeptide", "β-amyloid", and "β-amyloid protein" as used in claims 1, 3, 7 and 12-14, are indefinite because the recitations are not the same and the artisan cannot discern the difference in scope between the terms. As there are multiple "amyloid" peptides of various sequences and lengths recognized in the art, and the terms are not defined in the specification, the artisan can not discern the metes and bounds or difference in scope of the various recitations.

In addition, while applicant may be his or her own lexicographer, a term in a claim may not be given a meaning repugnant to the usual meaning of that term. See In re Hill, 161 F.2d

367, 73 USPQ 482 (CCPA 1947). The terms "amyloid protein/peptide" , "aggregated amyloid formation" , "aggregation" and "chimeric" in the claims are used by the claims to mean (roughly), any non-naturally occurring peptide which either forms amyloid or amyloid-like deposits, i.e., for example, is insoluble under physiological conditions, or which shares the characteristics of specific embodiments of the specification for example exhibiting a shift in spectral analysis as noted in Figures 1-2 and 4 for Sup35, while the accepted meaning is aggregated formation of amyloid proteins or amyloid fusion proteins, i.e., of amyloid peptides.

The term "aggregated amyloid formation" and "aggregation" as used in the claims are further indefinite because the specification's discussion of the terms include solubility, being "amyloid-like" or "amyloidogenic", see p. 5, lines 10-23, but such exemplary embodiment do not establish or define the interactions or conditions which are required for "aggregation" to occur. For example the recitation could indicate insolubility, spectral shift, self-binding or binding to an alternative peptide. It is noted that even the art recognizes various forms of amyloid fibril aggregation, see in particular Newcombe et al., Biochimica et Biophysica Acta, 104:480-486, 1965, Cordell et al., Hughes et al., and Findeis et al., of record, but as previously set forth the peptides which are aggregating are not even required to be amyloid peptides, and thus the artisan is left with no guidance as to the specific interaction which is required to occur. The specification fails to delineate that which is "amyloid-like" and thus the artisan could not readily discern any of the characteristics of amyloid protein interactions amongst those known, are sufficient or required. Thus, the artisan can not readily determine the metes and bounds of the

claims based on the prior art and the guidance provided in the specification and therefore clarification of the precise structural and or functional features and interactions is required.

Further, chimeric peptides are recognized in the art as fusion proteins. However, the specification describes "chimeric" peptides as "peptides that do not naturally occur together in a single peptide unit", see p. 5, lines 25-p.6, line 23 and thus the term alternatively encompasses any non-naturally occurring sequence, for example a mutated peptide by deletion, insertion or substitution which is not necessarily a fusion protein as recognized by the fusion of two known naturally occurring compounds to make a single non-naturally occurring compound..

Further compounding the indefinite nature of the claims is the recitation of an "aggregate forming domain" as claimed in claim 7. Proteins comprising an "aggregate forming domain" are loosely described in the specification at p. 5, line 25 - p. 6, line 13. Yet, the specification fails to provide the structural constraints of the domain and fails to clarify the functional requirements of the required "aggregation". For example, the domain may reference those peptide residues specifically bound to each other in the aggregate or may specify those regions which are protease resistant.

Thus, for the aforementioned reasons the skilled artisan cannot discern the metes and bounds, structural and functional limitations of the claims and clarification, in different terms is required.

Claim Rejections - 35 USC § 102

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claims 1, 3, 7, 12-13, and 17-18 stand rejected under 35 U.S.C. 102(b) as being anticipated by Hughes et al, PNAS, 93:2065-70, 1996.

Hughes et al teach claim 1, a yeast-two hybrid system as a method of identifying amyloid aggregation and aggregating domains which are capable of inhibiting amyloid aggregation, see abstract and Discussion, page 2068-9 and Figure 1. In these experiments Hughes identifies candidate substances (mutated forms of amyloid or alternate proteins) which inhibit the self-aggregation of amyloid peptides. Hughes explains that the kinetics of amyloid fibril formation by beta-amyloid is typical of a nucleation-dependent polymerization mechanism. This event was studied by investigating the interaction of monomers recognized by Hughes as nucleation-dependent aggregation which leads to fibril formation as depicted in Figure 1 and abstract, see in particular lines 1-5 and 13-30. Claims 3-4 are anticipated by Hughes et al as the aggregate-prone protein comprises β-amyloid chimeric proteins (LexA-Aβ fusion and B42-Aβ fusion, see Experimental Procedures). Claim 7 is anticipated as the chimeric protein comprises at least an aggregate forming domain and defines at least residues 19 and 20 as a domain critical to such aggregate formation of a mammalian amyloid polypeptide, operably attached to a detectable marker protein. The marker protein is the bait and prey constructs which lead to the expression

of reporter plasmids LEU2 and lacZ genes as disclosed at p. 2067, column 1-p. P. 2068 column 2, growth with leucine Beta-galactosidase. Claims 12-13 are anticipated as the amyloid polypeptide is β-amyloid and comprises at least about amino acids 1-42 . Claims 17-18 are anticipated as the aggregate is labeled with a chromophore (ECL detection, see Experimental procedures). Thus, claims 1, 3-4, 6-7, 12-13 and 17-18 are anticipated by Hughes et al.

11. Claims 1, 3, 12,-13, 15, 17-19 and 37 stand rejected under 35 U.S.C. 102(b) as being anticipated by Cordell et al, WO91/04339, 4 April, 1991.

Cordell et al teach assays and reagents for amyloid deposition including the identification of agents which inhibit amyloid formation. It is noted at p. 8, lines 20-34 that within the scope of the invention is modified beta amyloid proteins with one or more substituted amino acids. Thus as the specification defines chimeric proteins as non-naturally occurring, the substituted mutants apply as chimeric aggregate-prone amyloid proteins. The amyloid products produced may be expressed in yeast and include beta-amyloid 1-42 and preamyloid precursors, see in particular p. 6, lines 5-30 and p. 7, line 13 and p. 11, lines 3-28. The methods include screening compounds for inhibition of aggregate formation and the amyloid aggregates are detected by Congo red, thioflavin S or silver salt staining which are indicative of fibrillary material, in particular p. 13, lines 20-36. Aggregates may be detected by attachment of antibodies or other labels such as fluorescent enzymatic or radioactive (35S) labels, in particular, pps. 14-15, especially p. 15, lines 5-6 and 19-20. Thus, the reference teachings anticipate the claimed invention.

12. Claims 1, 3, 7, 12-13, 17-18 and 37 are rejected under 35 U.S.C. 102(e) as being anticipated by Findeis et al., US Patent No. 5,854,204 filed 3-14-1996.

Findeis et al., teach A-beta peptides including chimeric peptides as defined in the specification which differ from naturally occurring beta amyloid at one or more amino acids residues and including aggregating domains which are aggregating portions of beta-amyloid. Findeis also teach screening assays using such peptides to identify modulatory influences on amyloid aggregation, see in particular Abstract. The peptides are expressed in yeast cells in particular S. Cerevisiae as discloses at col. 38, lines 5, 12 and 60-65. The peptides may also be fusion proteins or chimeras as disclosed in the paragraph spanning columns 30-31. The proteins may be detected or labeled by biotinylation, labeled by fluorescence, or monitored in seeded assays, see in particular columns 31-33 and Example 6. The peptides include those of Tables I-VI and Examples 1-12 in particular. Thus the reference teachings anticipate the claimed invention

13. Claims 1, 7, 8, 17-18, 20 and 22 are rejected under 35 U.S.C. 102(b) as being anticipated by Patino et al., Science 273:622-26, 1996.

Patino et al., teach analysis of the aggregation and inhibition of aggregation of yeast cells expressing Sup35-green fluorescent protein labeled chimeric peptides in yeast cells and in yeast cells over expressing Hsp104, see in particular Abstract, Insolubility of Sup35 in PSI+ cells, Role of the chaperone Hsp104 in Sup35 aggregation and Figures 1-5. Hsp104 is a candidate agent which inhibits aggregation. It is also noted that Figure 1 includes the analysis of Hsp104 point

mutated peptides. While Sup35 is not an amyloid protein it qualifies as an aggregate-prone amyloid protein/peptide as Sup35 forms amyloid-like aggregates and aggregates in yeast cells exhibiting the PSI+ phenotype. Thus, the reference teachings anticipate the claimed invention.

Claim Rejections - 35 USC § 103

14. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

15. Claim 16 is rejected under 35 U.S.C. 103(a) as being unpatentable over Hughes et al, PNAS, 93:2065-70, 1996, Cordell et al, WO91/04339, 4 April, 1991, Findeis et al., US Patent No. 5,854,204 filed 3-14-1996 and Patino et al., Science 273:622-26, 1996 as set forth above in view of King et al., PNAS, 94(13):6618-22, June 24, 1997, Selvaggini et al., Biochem. & Biophys. Res. Comm., 1993 Aug 16, 194(3):1380-86.

Hughes et al., Cordell et al., Findeis et al., and Patino et al., are as set forth above and teach the method of claim 1.

Neither Hughes et al., Cordell et al., Findeis et al., nor Patino et al., teach the limitations of claim 16, the method of claim 1 wherein aggregation is detected by increased protease resistance.

King et al., and Selvaggini et al., each teach analysis of aggregation of aggregate prone amyloid proteins via protease resistance, see in particular Abstracts of both articles.

Thus, it would have been prima facie obvious to the skilled artisan that one could practice the method of claim 1 as taught by Hughes, Cordell, Findeis, and Patino with the modification of detecting aggregation via protease resistance as taught by King and Selvaggini. One of skill in the art would have been motivated to make such modification based on the ease of the assay and expectation of positive results using the assay as taught by King and Selvaggini. Thus, the cumulative reference teachings render the invention obvious.

16. Claims 9-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hughes et al, PNAS, 93:2065-70, 1996, Findeis et al., US Patent No. 5,854,204 filed 3-14-1996 and Patino et al., Science 273:622-26, 1996 as set forth above in view of Ogawa et al., PNAS 92(25):11899-903, 1995, Schilthuis et al., EMBO Journal, 12(9):3459-66, 1993 and Mohler et al., Somatic Cell & Mol. Genet., 20(3):153-62, 1994.

Hughes et al., Findeis et al., and Patino et al., are as set forth above and teach the method of claims 1 and 7.

Neither Hughes et al., Findeis et al., nor Patino et al., teach the limitations of claims 9-11, the method of claim 7 and 10 wherein the marker proteins are a drug-resistance marker protein, a hormone receptor protein and a glucocorticoid receptor protein.

Ogawa et al., teach a chimeric fusion marker protein marker where detection is achieved using green fluorescent protein linked to glucocorticoid receptor as a marker of dexamethasone induced translocation to the nucleus, see in particular Abstract..

Schilthuis et al., teach a chimeric fusion protein marker where detection is achieved using the thyroid hormone receptor for detection via transcription activation with thyroid hormone T3, see in particular Abstract.

Mohler et al., teach a chimeric fusion protein marker where detection is achieved using the gene for membrane-bound neomycin phosphotransferase for the conferrance of drug resistance, see in particular Abstract.

Thus, it would have been prima facie obvious to the skilled artisan that one could practice the method of claims 1 and 7 as taught by Hughes, Findeis, and Patino with the modification of a chimeric fusion marker protein for the glucocorticoid receptor as taught by Ogawa, the thyroid hormone receptor as taught by Schilthuis or a drug resistance marker protein as taught by Mohler for the detection marker of aggregation. One of skill in the art would have been motivated to make such modification based on the detection achieved and expectation of positive results using the detection assays as taught by Ogawa, Schilthuis and Mohler. Thus, the cumulative reference teachings render the invention obvious.

Status of Claims

17. No claims are allowed.

Conclusion

18. Any inquiry of a general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for Group 1600 is (703) 308-4242.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sharon L. Turner, Ph.D. whose telephone number is (703) 308-0056. The examiner can normally be reached on Monday-Friday from 8:00 AM to 4:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached at (703) 308-4623.

Sharon L. Turner, Ph.D.
April 18, 2002

Gary L. Kunz
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